

PATENT SPECIFICATION

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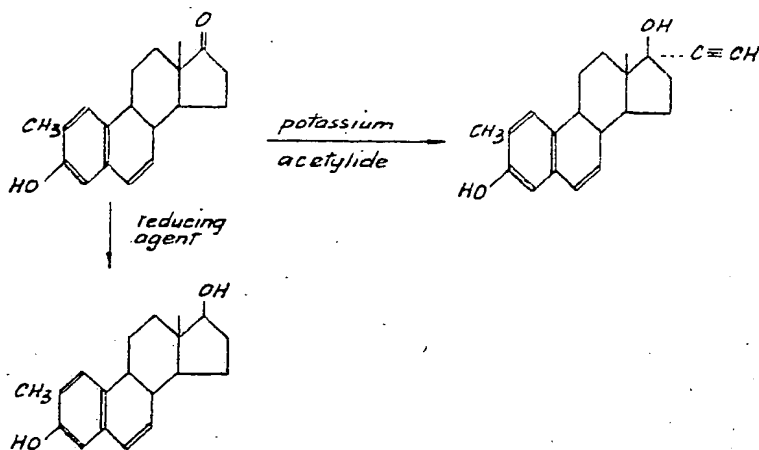
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COMPLETE SPECIFICATION

Cyclopentanophenanthrene Derivatives and process for the Production thereof

- We, SYNTEX S.A., Apartado Postal 2679, Mexico City, Mexico, a Corporation of Mexico, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
- The present invention relates to cyclopentanophenanthrene compounds and to a process for the production thereof.
- The present invention relates especially to novel 2-methyl estrone and estradiol derivatives and to a novel process for the production thereof. The novel compounds of the present invention are estrogenic hormones generally suitable for the treatment of prostate cancer, i.e., they show lesser estrogenic activity together with valuable anti-androgenic activity.
- In our application 16962/57 (Serial No. 857,080) there is disclosed the production of 2 - methyl - $\Delta^{1,4,6}$ - androstatriene - 3,17 - dione. In accordance with the present invention it has been discovered that this compound when subjected to pyrolysis at approximately 600° C. aromatizes to form 2-methyl-6-dehydro-estrone, an estrogenic hormone and intermediate for the production of other novel 2-methyl-estrone and estradiol derivatives. These are 2 - methyl - 6 - dehydro-estradiol, 2 - methyl - 17 α - ethinyl - 6 - dehydro-estradiol, 2 - methyl - estrone, 2 - methyl-estradiol, and 2 - methyl - 17 α - ethinyl-estradiol compounds. From these compounds by conventional means there may also be prepared their novel esters of hydrocarbon carboxylic acids of less than 12 carbon atoms.
- The novel 2-methyl estrone and estradiol derivatives of the present invention may therefore be represented by the following formulae.

[Price 3s. 6d.]

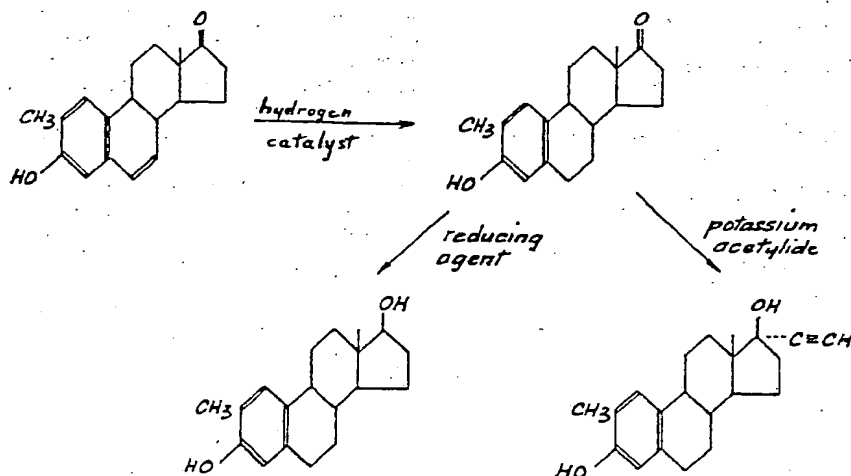


To prepare the ethynyl derivative as indicated above the 17-keto compound may be reacted with potassium acetylide prepared *in situ*. Thus the 2-methyl-6-dehydro-estrone may be dissolved in an organic solvent, such as benzene, and added to a solution of potassium metal in a tertiary alcohol such as *t*-butyl alcohol. Acetylene is then passed into the reaction mixture for a prolonged period of time of the order of 2 days. Neutralization with acid and removal of the organic solvents by steam distillation results in a precipitate of the 17α-ethynyl product which is purified,

e.g., by crystallization.

For the production of the estradiol derivative the estrone compound is treated with a reducing agent, preferably an alkali metal hydride such as sodium borohydride or lithium aluminium hydride in alcohol-water solution.

Similarly with prior hydrogenation the 2-methyl-6-dehydroestrone can be utilized for the preparation of 2-methyl-estrone, 2-methyl-estradiol and 2-methyl-17α-ethynyl-estradiol in accordance with the following scheme:



As indicated above hydrogenation in the presence of a hydrogenation catalyst, preferably palladium or platinum, until 1 mol of hydrogen is taken up gives the corresponding 2-methyl-estrone. Reaction with a reducing agent or with potassium acetylide as previously described in connection with the 6-dehydro compounds gives the corresponding 2-methyl estradiol and 17α-ethynyl-estradiol derivatives.

It may be noted further that all of the non-tertiary alcohol groups in both the 6-dehydro and corresponding 6-saturated compounds previously described may be conventionally esterified as with acid anhydrides or acyl halides to give either mono or diesters as previously indicated.

The following specific examples serve to illustrate but are not intended to limit the present invention.

10. 2-Methyl-17 α -ethinyl-estradiol or an ester thereof with a hydrocarbon carboxylic acid of less than 12 carbon atoms.

MEWBURN ELLIS & CO.,
Chartered Patent Agents,
70 & 72, Chancery Lane, London, W.C.2,
Agents for the Applicants.

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